Complete Summary

GUIDELINE TITLE

Treatment and prevention of heparin-induced thrombocytopenia. American College of Chest Physicians evidence-based clinical practice guidelines (8th edition).

BIBLIOGRAPHIC SOURCE(S)

Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):340S-80S. [284 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):311S-37S.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- December 3, 2008, Innohep (tinzaparin): The U.S. Food and Drug Administration (FDA) has requested that the labeling for Innohep be revised to better describe overall study results which suggest that, when compared to unfractionated heparin, Innohep increases the risk of death for elderly patients (i.e., 70 years of age and older) with renal insufficiency. Healthcare professionals should consider the use of alternative treatments to Innohep when treating elderly patients over 70 years of age with renal insufficiency and deep vein thrombosis (DVT), pulmonary embolism (PE), or both.
- February 28, 2008, Heparin Sodium Injection: The U.S. Food and Drug Administration (FDA) informed the public that Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection and their heparin lock flush solutions. Alternate heparin manufacturers are expected to be able to increase heparin production sufficiently to supply the U.S. market. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with

symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Heparin-induced thrombocytopenia (HIT) with and without associated thrombosis

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Anesthesiology
Cardiology
Critical Care
Emergency Medicine
Family Practice
Hematology
Internal Medicine
Oncology
Orthopedic Surgery
Pharmacology
Pulmonary Medicine
Surgery
Thoracic Surgery

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel

Health Care Providers
Hospitals
Nurses
Patients
Pharmacists
Physician Assistants
Physicians
Psychologists/Non-physician Behavioral Health Clinicians
Social Workers

GUIDELINE OBJECTIVE(S)

- To describe the recognition, treatment, and prevention of heparin-induced thrombocytopenia (HIT)
- To update evidence-based recommendations for the use of antithrombotic and thrombolytic therapy for the management of thromboembolic conditions associated with HIT or suspected HIT

TARGET POPULATION

- Patients receiving heparin in whom the clinician considers at risk of heparin-induced thrombocytopenia (HIT) or the exposure history of the patient is uncertain
- Patients who are starting unfractionated heparin (UFH) or low molecular weight heparin (LMWH) treatment and who have received UFH within the past 100 days, or those patients in whom exposure history is uncertain
- Patients in whom acute inflammatory, cardiorespiratory, neurologic, or other unusual symptoms and signs develop within 30 minutes of receiving intravenous bolus unfractionated heparin or subcutaneous low-molecular-weight heparin
- Postoperative patients receiving UFH antithrombotic prophylaxis
- Patients in whom HIT is rare (<0.1%); is uncommon (0.1-1.0%); is common (>1.0%)
- Patients undergoing cardiopulmonary bypass (CPB) surgery with acute or subacute HIT or a history of HIT
- Patients undergoing percutaneous coronary interventions (PCIs)

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment

1. Vitamin K antagonists (VKAs)*
2. Heparin or low-molecular-weight heparin (LMWH)
3. Nonheparin Anticoagulants
    - Danaparoid
    - Lepirudin
    - Argatroban
    - Fondaparinux
    - Bivalirudin
4. Reversal of VKAs
    - Vitamin K
    - Fresh frozen plasma

- Prothrombin complex concentrate (PCC)
- Recombinant factor VIIa

*__Note__: Since warfarin is the most commonly used VKA worldwide, warfarin was used interchangeably with VKA or coumarin.

Management

1. Platelet count monitoring
2. Heparin-dependent antibody testing
3. Activated partial thromboplastin time (APTT) monitoring
4. Prothrombin time (PT) monitoring
5. Systematic international normalized ratio (INR) monitoring
6. Follow-up

MAJOR OUTCOMES CONSIDERED

- Mortality
- Incidence of thrombosis
- Recurrent thromboembolism
- Limb amputation
- Incidence of major and minor hemorrhage
- Time to achieve therapeutic international normalized ratio (INR)
- Anticoagulant response
- Maintenance dose
- Time in the therapeutic range (TTR)
- Cost effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Process of Searching for Evidence

Defining the clinical question provided the framework for formulating eligibility criteria that guided the search for relevant evidence. In specifying eligibility criteria, authors identified not only patients, interventions, and outcomes, but also methodologic criteria. For many recommendations, authors restricted eligibility to randomized controlled trials (RCTs).

For many questions, randomized trials did not provide sufficient data, and chapter authors included observational studies when randomized trials were not the most appropriate design to address the research question. In particular, randomized trials are not necessarily the best design to understand risk groups, that is, the baseline or expected risk of a given event for certain subpopulations. Because no

interventions are typically examined in questions about prognosis, one replaces interventions by the duration of exposure measured in time.

Identifying the Evidence

To identify the relevant evidence, a team of librarians and research associates at the McMaster University Evidence based practice center (EPC) conducted comprehensive literature searches. Methodologic experts (including the editors) and the EPC librarians reviewed each question to ensure the development of a comprehensive search strategy. For example, for questions about antiplatelet agents, the EPC consulted chapter authors to ensure that the search included all relevant antiplatelet agents. More specifically, authors then decided whether to include dipyridamole in a search that already included aspirin, clopidogrel, and ticlopidine.

For each question the authors provided, the librarians searched the Cochrane Database of Systematic Reviews, MEDLINE, and Embase for published English-language literature and human studies between 2002 and May 2006. To filter MEDLINE and Embase search results for RCT evidence, the librarians used the search strategy developed by the Cochrane Collaboration. These searches updated the more comprehensive and sensitive searches conducted for the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines.

The EPC team conducted separate searches for systematic reviews; RCTs; and, if applicable, observational studies. For observational studies, searches were not restricted in terms of methodology. Although increasing the probability of identifying all published studies, this sensitive approach resulted in large numbers of citations for many of the defined clinical questions. Therefore, trained research assistants screened the citation list developed from the search using criteria of increased specificity to reduce the number of irrelevant citations that the authors received. These irrelevant citations included press news, editorials, narrative reviews, single-case reports, studies that included fewer participants than specified by authors as an inclusion criterion, animal studies (any nonhuman studies), and letters to the editor. Authors did not include data from abstracts of meetings for the development of recommendations, and the guideline developers did not explicitly use Internet sources to search for research data. Authors were encouraged, however, to mention abstracts that reported on groundbreaking data that were particularly relevant to a specific question in the chapters in order to alert readers that new, fully published evidence might become available shortly.

Standard Consideration of Study Quality

High-quality clinical guidelines should pay careful attention to the methodologic quality of the studies that form the basis of their recommendations. Using the example of the prevention of venous thromboembolism during air travel, Table 1 in the methodology companion (see "Availability of Companion Documents" field) shows the criteria for assessment of study quality (randomization, concealment or treatment allocation, blinding, completeness of follow-up, and whether the analysis was performed according to the intention-to-treat principle), and Table 2 in the methodology companion (see "Availability of Companion Documents" field) shows the presentation of results that were circulated to the authors. Whereas all

authors attended to these criteria, the guideline developers have summarized the results of the quality assessment for only a minority of the recommendations. Readers can find these summaries in an online appendix to the recommendations (see online supplemental data).

In assessing the quality of observational studies, the guideline developers did not make a distinction between prospective and retrospective because the key issues are unbiased sampling, high-quality measurement of patient characteristics and outcomes, and complete follow-up.

Although it is more likely that these quality criteria will be achieved in prospective studies, prospective studies may fail to achieve them, and retrospective studies may succeed. The guideline developers did make a key distinction about whether internal comparisons exist and their nature. Studies without internal comparisons received the label "case series" unless they met the following criteria: (1) a protocol existed before the date of commencement of data collection; (2) a definition of inclusion and exclusion criteria was available; (3) the study reported the number of excluded patients; (4) the study conducted a standardized follow-up, including description of schedule of follow-up, investigation of suspected outcomes, and criteria used to define outcomes; and (5) the study reported all losses to follow-up.

The guideline developers labeled studies that met these criteria "cohort studies without internal controls." Studies with internal comparisons received the label "cohort studies with concurrent controls" or "cohort studies with historical controls." These cohort studies may succeed or fail to ensure settings, similar time frames, adjustment for differences in patients' characteristics, and follow-up with patients. These features were captured in descriptive tables provided to authors when requested from the EPC.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) and the methodological quality of the underlying evidence (A, B, or C). See "Grades of recommendations for antithrombotic agents" in the "Availability of Companion Documents" field and the "Rating Scheme for the Strength of the Recommendations." field.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Summarizing Evidence

The electronic searches also included searches for systematic reviews. If authors were satisfied with a recent high-quality systematic review, evidence from that review provided a foundation for the relevant recommendation.

Pooled analyses from high-quality systematic reviews formed summary data on which panelists based their recommendations wherever possible. Pooling offers the advantage of obtaining more precise estimates of treatment effects and allows for greater generalizability of results. However, pooling also bears the risk of spurious generalization. In general, the summary estimates of interest were the different types of outcomes conveying benefits and downsides (risk, burden, and cost). When pooled estimates of effects were not available, the McMaster University Evidence based practice center (EPC) conducted metaanalysis to obtain pooled estimates for specific questions. These were questions that authors had specifically identified.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Group-Specific Recommendations

In general, the guideline developers have endeavored to make their recommendations as specific as possible for patient subgroups differing according to risk. Whenever valid prognostic data were available, the guideline developers used them to estimate absolute effects and made recommendations accordingly. Unfortunately, reliable prognostic indexes are not usually available, limiting the extent to which such group-specific recommendations are possible.

Acknowledge Values and Preferences and Resource Use Underlying Recommendations

Under ideal circumstances, knowledge of average patient values and preferences would be available for every recommendation, the panel members would summarize these values and preferences, and they would be integrated into the recommendations that guideline developers make. The guideline developers asked all chapter chairs before beginning the searches for the relevant literature to identify recommendations that they believed were particularly sensitive to patients' values and preferences. Moderate-quality evidence regarding values and preferences bearing directly on the recommendations proved available for only the chapter that addresses antithrombotic therapy in patients with atrial fibrillation. The panelists bore in mind what average patient values and preferences may be; the process, however, is speculative.

The guideline developer's main strategy for dealing with this unsatisfactory situation is to make the values and preferences underlying the recommendations explicit whenever the panelists believed that value and preference issues were crucial for a recommendation.

In addition, the guideline developers involved three consultants with expertise in the area of values and preferences to collaborate with the chairs of two chapters and try to ensure that the guidelines adequately represented the views of patients. This collaboration led to extensive discussions among the chapter authors and the consultants and the reflection of these discussions in the associated values and preference statements.

Finalizing and Harmonizing Recommendations

After having completed the steps the guideline developers have described above, the guideline authors formulated draft recommendations before the conference, which laid the foundation for authors to work together and critique the recommendations. Figure 1 in the methodology companion (see "Availability of Companion Documents" field) shows the process of guideline development and review. Drafts of chapters that included draft recommendations were usually distributed for peer review to at least two panel members and were always reviewed by at least one panel editor before the conference. Written critiques were prepared and returned to the authors for revision of their work. At the plenary conference, a representative of each chapter presented potentially controversial issues in their recommendations. Chapter authors met to integrate feedback and consider related recommendations in other chapters and to revise their own guidelines accordingly. Authors continued this process after the conference until they reached agreement within their groups and with other author groups who provided critical feedback. The editors of this supplement harmonized the chapters and resolved remaining disagreements between chapters through facilitated discussion. All major correspondence and discussions at the meeting were recorded in written and audio protocols and are publicly available.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading Recommendation			
Grade of Recommendation*	**Benefit vs. Risk and Burdens**	**Methodologic Quality of Supporting Evidence**	**Implications**
Strong recommendation, high-quality evidence, Grade 1A	Desirable effects clearly outweigh undesirable effects, or *vice versa*	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; further research is very unlikely to change our confidence in the estimate of effect

Grading Recommendation			
Grade of Recommendation*	**Benefit vs. Risk and Burdens**	**Methodologic Quality of Supporting Evidence**	**Implications**
Strong recommendation, moderate-quality evidence, Grade 1B	Desirable effects clearly outweigh undesirable effects, or *vice versa*	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, low or very low-quality evidence, Grade 1C	Desirable effects clearly outweigh undesirable effects, or *vice versa*	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak recommendation, high-quality evidence, Grade 2A	Desirable effects closely balanced with undesirable effects	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient or society values; further research is very unlikely to change our confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade 2B	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Best action may differ depending on circumstances or patient or society values; higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Weak recommendation, low or very low-quality evidence, Grade 2C	Desirable effects closely balanced	Evidence for at least one critical outcome from observational studies, case series,	Other alternatives may be equally reasonable; higher-quality research is likely to have an

Grading Recommendation			
Grade of Recommendation*	**Benefit vs. Risk and Burdens**	**Methodologic Quality of Supporting Evidence**	**Implications**
	with undesirable effects	or from RCTs with serious flaws or indirect evidence	important impact on our confidence in the estimate of effect and may well change the estimate

*The guideline developers use the wording *recommend* for strong (Grade 1) recommendations and *suggest* for weak (Grade 2) recommendations.

COST ANALYSIS

For these guidelines, the guideline developers implemented recommendations of a recent American College of Chest Physicians (ACCP) task force on integrating resource allocation in clinical practice guidelines by restricting resource expenditure consideration to a small number of recommendations for which they were particularly relevant. The guideline developers relied on two consultants with expertise in economic assessment to help with the process of considering costs in those small numbers of recommendations that the guideline developers considered very important to the decision.

Recommendations highly sensitive to resource allocation now include value and preference statements regarding how cost issues were integrated.

Refer to "Strategies for incorporating resource allocation and economic considerations" (see "Availability of Companion Documents" field) for details of the cost analyses.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The American College of Chest Physicians (ACCP) Health Science Policy (HSP) established a process for the thorough review of all ACCP evidence-based clinical practice guidelines. After final review by the editors, the guidelines underwent review by appropriate NetWorks of the ACCP (for these guidelines, the Cardiovascular and Pulmonary Vascular NetWorks), the HSP, and the Board of Regents. The latter two have the right of approval or disapproval but usually work with the guideline authors and editors to make necessary revisions before final approval. Each group identified primary reviewers who read the full set of chapters as well as individual committee members who were responsible for reviewing one or more chapters. The reviewers considered both content and methodology as well as whether there was balanced, not biased, reporting and

adherence to HSP processes. Finally, the *CHEST* editor-in-chief read and forwarded the manuscripts for nonbiased, independent, external peer review before acceptance for publication.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The grades of recommendation (1A, 1B, 1C, 2A, 2B, 2C) are defined at the end of the "Major Recommendations" field.

Recognition of Heparin-Induced Thrombocytopenia (HIT)

Platelet Count Monitoring for HIT

For patients receiving heparin in whom the clinician considers the risk of heparin-induced thrombocytopenia (HIT) to be > 1.0%, the guideline developers recommend platelet count monitoring over no platelet count monitoring **(Grade 1C)**. For patients receiving heparin who have an estimated risk of HIT of 0.1 to 1.0%, the guideline developers suggest platelet count monitoring over no platelet count monitoring **(Grade 2C)**.

Platelet Count Monitoring of Patients Recently Treated With Heparin

For patients who are starting unfractionated heparin (UFH) or low molecular weight heparin (LMWH) treatment and who have received UFH within the past 100 days, or those patients in whom exposure history is uncertain, the guideline developers recommend obtaining a baseline platelet count and then a repeat platelet count within 24 hours of starting heparin over not obtaining a repeat platelet count **(Grade 1C)**.

Anaphylactoid Reactions After IV UFH Bolus

For patients in whom acute inflammatory, cardiorespiratory, neurologic, or other unusual symptoms and signs develop within 30 minutes following an intravenous (IV) UFH bolus, the guideline developers recommend performing an immediate platelet count measurement, and comparing this value to recent prior platelet counts, over not performing a platelet count **(Grade 1C)**.

Platelet Count Monitoring in Patients Receiving Therapeutic-Dose UFH

For patients who are receiving therapeutic-dose UFH, the guideline developers suggest platelet count monitoring at least every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first) over less frequent platelet count monitoring **(Grade 2C)**.

Platelet Count Monitoring in Postoperative Patients Receiving UFH Antithrombotic Prophylaxis (Highest Risk Group for HIT)

For patients who are receiving postoperative antithrombotic prophylaxis with UFH (i.e., the patient population at highest risk for HIT [HIT risk > 1%]), the guideline developers suggest at least every-other-day platelet count monitoring between postoperative days 4 to 14 (or until UFH is stopped, whichever occurs first) over less frequent platelet count monitoring **(Grade 2C)**.

Platelet Count Monitoring in Patients in Whom HIT Is Infrequent (0.1 to 1%)

For medical/obstetrical patients who are receiving prophylactic-dose UFH, postoperative patients receiving prophylactic-dose LMWH, postoperative patients receiving intravascular catheter UFH "flushes," or medical/obstetrical patients receiving LMWH after first receiving UFH (estimated HIT risk, 0.1 to 1%), the guideline developers suggest platelet count monitoring at least every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first), when practical, over less frequent platelet count monitoring **(Grade 2C)**.

Platelet Count Monitoring When HIT Is Rare (< 0.1%): UFH and LMWH

For medical/obstetrical patients who are receiving only LMWH, or medical patients who are receiving only intravascular catheter UFH flushes (HIT risk < 0.1%), the guideline developers suggest clinicians do not use routine platelet count monitoring **(Grade 2C)**.

Platelet Count Monitoring When HIT Is Rare (< 0.1%): Fondaparinux

For patients who are receiving fondaparinux thromboprophylaxis or treatment, the guideline developers recommend that clinicians do not use routine platelet count monitoring **(Grade 1C)**.

Management of Patients in Whom Platelet Counts Are Not Monitored

In outpatients who will receive heparin prophylaxis or treatment, informed consent should include HIT and its typical sequelae (new thrombosis, skin lesions), and the patient should be advised to seek medical advice if these events occur **(Grade 2C)**.

Screening for Subclinical HIT Antibody Seroconversion

In patients who receive heparin, or in whom heparin treatment is planned (e.g., for cardiac or vascular surgery), the guideline developers recommend against routine HIT antibody testing in the absence of thrombocytopenia, thrombosis, heparin-induced skin lesions, or other signs pointing to a potential diagnosis of HIT **(Grade 1C)**.

When Should HIT Be Suspected?

For patients who are receiving heparin or have received heparin within the previous 2 weeks, the guideline developers recommend investigating for a diagnosis of HIT if the platelet count falls by $\geq$50%, and/or a thrombotic event occurs, between days 5 and 14 (inclusive) following initiation of heparin, even if

the patient is no longer receiving heparin therapy when thrombosis or thrombocytopenia has occurred **(Grade 1C)**.

Special Situation: Anticoagulant Prophylaxis and Platelet Count Monitoring After Cardiac Surgery

For postoperative cardiac surgery patients, the guideline developers recommend investigating for HIT antibodies if the platelet count falls by ≥50%, and/or a thrombotic event occurs, between postoperative days 5 and 14 (inclusive; day of cardiac surgery = day 0) **(Grade 1C)**.

Treatment of HIT

Nonheparin Anticoagulants for Treating HIT (With or Without Thrombosis)

1. For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, the guideline developers recommend use of an alternative, nonheparin anticoagulant (danaparoid **[Grade 1B]**, lepirudin **[Grade 1C]**, argatroban **[Grade 1C]**, fondaparinux **[Grade 2C]**, bivalirudin **[Grade 2C]** over the further use of UFH or LMWH therapy or initiation/continuation of a VKA **(Grade 1B)**.
2. For patients receiving lepirudin, the initial lepirudin infusion rate should be no higher than 0.10 mg/kg/h (patients with creatinine < 90 microgram-mol/L), with lower infusion rates for patients with higher serum creatinine levels (creatinine, 90 to 140 microgram-mol/L: starting infusion rate, 0.05 mg/kg/h; creatinine, 140 to 400 microgram-mol/L: starting infusion rate, 0.01 mg/kg/h; creatinine > 400 microgram-mol/L: starting infusion rate, 0.005 mg/kg/h) **(Grade 1C)**. Furthermore, the guideline developers recommend that the initial IV bolus either be omitted or, in case of perceived life- or limb-threatening thrombosis, be given at a reduced dose (0.2 mg/kg) **(Grade 1C)**. Further, the guideline developers recommend that APTT monitoring be performed at 4-hour intervals until it is apparent that steady state within the normal range (1.5 to 2.0 times patient baseline [or mean laboratory] APTT) is achieved **(Grade 1C)**.
3. When argatroban is used to treat patients who have heart failure, multiple organ system failure, or severe anasarca, or who are postcardiac surgery, the guideline developers suggest beginning the initial infusion at a rate between 0.5 and 1.2 micrograms/kg/minute with subsequent adjustments using the APTT, over the usual recommended starting dose of 2.0 micrograms/kg/min **(Grade 2C)**.
4. When danaparoid is used to treat patients with strongly suspected (or confirmed) HIT, the guideline developers recommend a therapeutic-dose regimen (see text) administered (at least initially) by the IV route over prophylactic-dose regimens or initial subcutaneous (SC) administration **(Grade 1B)**.
5. For patients with strongly suspected or confirmed HIT, whether or not there is clinical evidence of lower-limb deep vein thrombosis (DVT), the guideline developers recommend routine ultrasonography of the lower-limb veins for investigation of DVT over not performing routine ultrasonography **(Grade 1C)**

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Vitamin K Antagonists (VKAs)

Management of Direct Thrombin Inhibitor-VKA Overlap

For patients with strongly suspected or confirmed HIT, the guideline developers recommend against the use of VKA (coumarin) therapy until after the platelet count has substantially recovered (i.e., usually to at least 150 x 10^9/L) over starting VKA therapy at a lower platelet count **(Grade 1B)**; that VKA therapy be started only with low, maintenance doses (maximum, 5 mg of warfarin or 6 mg of phenprocoumon) rather than with higher initial doses **(Grade 1B)**; and that the nonheparin anticoagulant (e.g., lepirudin, argatroban, danaparoid) be continued until the platelet count has reached a stable plateau, the international normalized ration (INR) has reached the intended target range, and after a minimum overlap of at least 5 days between nonheparin anticoagulation and VKA therapy rather than a shorter overlap **(Grade 1B)**.

Reversal of VKA Anticoagulation

For patients receiving a VKA at the time of diagnosis of HIT, the guideline developers recommend use of vitamin K (10 mg by mouth [po] or 5 to 10 mg IV) **(Grade 1C)**.

LMWH for HIT

For patients with strongly suspected HIT, whether or not complicated by thrombosis, the guideline developers recommend against use of LMWH **(Grade 1B)**.

Prophylactic Platelet Transfusions for HIT

For patients with strongly suspected or confirmed HIT who do not have active bleeding, the guideline developers suggest that prophylactic platelet transfusions should not be given **(Grade 2C)**.

Special Patient Populations

Patients With Previous HIT Undergoing Cardiac or Vascular Surgery

1. For patients with a history of HIT who are HIT antibody negative and require cardiac surgery, the guideline developers recommend the use of UFH over a nonheparin anticoagulant **(Grade 1B)**.
2. For patients with a history of HIT who are antibody positive by platelet factor 4 (PF4)-dependent enzyme immunoassay (EIA) but antibody negative by washed platelet activation assay, the guideline developers recommend the use of UFH over a nonheparin anticoagulant **(Grade 2C)**.

Remark: Preoperative and postoperative anticoagulation, if indicated, should be given with a nonheparin anticoagulant.

Patients With Acute or Subacute HIT Undergoing Cardiac Surgery

1. For patients with acute HIT (thrombocytopenic, HIT antibody positive) who require cardiac surgery, the guideline developers recommend one of the following alternative anticoagulant approaches (in descending order of preference): delaying surgery (if possible) until HIT has resolved and antibodies are negative or weakly positive (See the "Patients With Previous HIT Undergoing Cardiac or Vascular Surgery" recommendations above) **(Grade 1B)**; using bivalirudin for intraoperative anticoagulation during cardiopulmonary bypass (if techniques of cardiac surgery and anesthesiology have been adapted to the unique features of bivalirudin pharmacology) **(Grade 1B)** or during "off-pump" cardiac surgery **(Grade 1B)**; using lepirudin for intraoperative anticoagulation (if ECT is available and patient has normal renal function and is judged to be at low risk for postcardiac surgery renal dysfunction) **(Grade 2C)**; using UFH plus the antiplatelet agent epoprostenol (if ECT monitoring is not available or renal insufficiency precludes lepirudin use) **(Grade 2C)**; using UFH plus the antiplatelet agent, tirofiban **(Grade 2C)**; or using danaparoid for intraoperative anticoagulation for off-pump coronary artery bypass surgery **(Grade 2C)** over performing the surgery with UFH when platelet-activating anti-PF4/heparin antibodies are known to be present in a patient with acute or recent HIT.
2. For patients with subacute HIT (platelet count recovery, but continuing HIT antibody positive), the guideline developers recommend delaying surgery (if possible) until HIT antibodies (washed platelet activation assay) are negative, then using heparin (See the "Patients With Previous HIT Undergoing Cardiac or Vascular Surgery" recommendation above) over using a nonheparin anticoagulant **(Grade 1C)**. If surgery cannot be delayed, the guideline developers suggest the use of a nonheparin anticoagulant (See the recommendation above) over the use of UFH **(Grade 2C)**.

Percutaneous Coronary Intervention (PCI)

1. For patients with strongly suspected (or confirmed) acute HIT who require cardiac catheterization or PCI, we recommend a nonheparin anticoagulant (bivalirudin **[Grade 1B]**, argatroban **[Grade 1C]**, lepirudin **[Grade 1C]** or danaparoid **[Grade 1C]**), over UFH or LMWH **(Grade 1B)**.
2. For patients with previous HIT (who are antibody negative) who require cardiac catheterization or PCI, the guideline developers suggest use of a nonheparin anticoagulant (See the recommendation above) over UFH or LMWH **(Grade 2C)**.

Definitions:

Grading Recommendation			
Grade of Recommendation*	**Benefit vs. Risk and Burdens**	**Methodologic Quality of Supporting Evidence**	**Implications**
Strong recommendation, high-quality evidence, Grade 1A	Desirable effects clearly outweigh	Consistent evidence from RCTs without important limitations or	Recommendation can apply to most patients in most circumstances; further research is very

Grading Recommendation			
Grade of Recommendation*	**Benefit vs. Risk and Burdens**	**Methodologic Quality of Supporting Evidence**	**Implications**
	undesirable effects, or *vice versa*	exceptionally strong evidence from observational studies	unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate-quality evidence, Grade 1B	Desirable effects clearly outweigh undesirable effects, or *vice versa*	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, low or very low-quality evidence, Grade 1C	Desirable effects clearly outweigh undesirable effects, or *vice versa*	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak recommendation, high-quality evidence, Grade 2A	Desirable effects closely balanced with undesirable effects	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient or society values; further research is very unlikely to change our confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade 2B	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Best action may differ depending on circumstances or patient or society values; higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate

Grading Recommendation			
Grade of Recommendation*	**Benefit vs. Risk and Burdens**	**Methodologic Quality of Supporting Evidence**	**Implications**
Weak recommendation, low or very low-quality evidence, Grade 2C	Desirable effects closely balanced with undesirable effects	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate

*The guideline developers use the wording *recommend* for strong (Grade 1) recommendations and *suggest* for weak (Grade 2) recommendations.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate prevention, monitoring, management of patients with heparin-induced thrombocytopenia (HIT)

POTENTIAL HARMS

- Heparin-induced thrombocytopenia (HIT) is an antibody-mediated adverse effect of heparin that is important because of its strong association with venous and arterial thrombosis. Patients treated with heparin in whom HIT develops constitute a cohort with substantially increased thrombotic risk, both in relative (odds ratio [OR] for thrombosis, 20 to 40) and absolute (thrombosis risk, 30 to 75%) terms, depending on the patient population affected.
- Nonheparin anticoagulants have a relatively high risk of bleeding; there is the potential for treatment-related adverse events as a consequence of platelet count monitoring.

- HIT is a prothrombotic condition that is associated with increased *in vivo* thrombin generation (as evidenced by the presence of elevated levels of thrombin-antithrombin complexes) and thus can be considered an acquired, hypercoagulability syndrome.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Given the availability of nonheparin anticoagulants to treat heparin-induced thrombocytopenia (HIT), low molecular-weight heparin (LMWH) should be considered contraindicated for treatment of acute HIT.
- Warfarin therapy is contraindicated during the acute phase of HIT, i.e., the guideline developers recommend against the use of vitamin K antagonist (VKA) (coumarin) therapy until after the platelet count has substantially recovered (i.e., usually to at least 150 x 10^9/L) over starting VKA therapy at a lower platelet count; furthermore, when warfarin is introduced, this should be done only with low, maintenance doses (maximum, 5 mg of warfarin) rather than with higher initial doses; and the overlapping nonheparin anticoagulant (e.g., lepirudin, argatroban, danaparoid) should be continued until the platelet count has reached a stable plateau, the INR has reached the intended target range, and after a minimum overlap of at least 5 days between nonheparin anticoagulation and warfarin therapy rather than a shorter overlap.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Limitations of These Guideline Development Methods

Limitations of these guidelines include the limited quantity and quality of available studies for some patient groups. Second, it is possible that some authors followed this methodology more closely than others, although the development process was centralized by an evidence-based practice center (EPC) and supervised by the editors. Third, it is possible that the guideline developers missed relevant studies in spite of the comprehensive searching process. Fourth, despite their efforts to begin centralizing the methodologic evaluation of all studies to facilitate uniformity in the validity assessments of the research incorporated into these guidelines, resources were insufficient to conduct this evaluation for all but a few of the recommendations in each chapter. Fifth, the guideline developers performed only few statistical pooling exercises of primary study results. Finally, sparse data on patient preferences and values represent additional limitations inherent to most guideline development methods.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy includes local educational programs and tools offered through the American College of Chest Physicians (ACCP) Board of Governors and select other locations. The Veterans Administration (VA) will also participate in a pilot project.

IMPLEMENTATION TOOLS

Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Safety
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):340S-80S. [284 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Sep (revised 2008 Jun)

GUIDELINE DEVELOPER(S)

American College of Chest Physicians - Medical Specialty Society

SOURCE(S) OF FUNDING

American College of Chest Physicians

GUIDELINE COMMITTEE

American College of Chest Physicians (ACCP) Expert Panel on Antithrombotic and Thrombolytic Therapy

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Warkentin discloses that he has received grant monies from the Heart & Stroke Foundation of Ontario, as well as industry-related sources of Organon and GlaxoSmithKline. Dr. Warkentin also received consultant fees from Organon, GlaxoSmithKline, and GTI, Inc, and has served on the speakers bureaus of Organon, GlaxoSmithKline, Sanofi-Aventis.

Professor Greinacher discloses that he has received grant monies from projects funded by Graduiertenkolleg, BMBF, Krupp-Kolleg, and EFRE, and has been involved with industry projects such as the development of danaparoid (Orgaran) in heparin-induced thrombocytopenia and performed product evaluations of the PIFA Heparin/PF4 Rapid Assay.

Dr. Lincoff discloses that he has received grant monies from The Medicines Company, Sanofi, Lilly, Pfizer, Schering-Plough, and AstraZeneca. He is also on advisory committees for Sanofi, The Medicines Company, and Pfizer.

Professor Koster discloses that he has received consultant fees from The Medicines Company, and that he is on the speakers bureaus for the Medicines Company and Mitsubishi Pharma Europe. Professor Koster also has received fees from The Medicines Company.

ENDORSER(S)

American College of Clinical Pharmacy - Medical Specialty Society
American Society of Health-System Pharmacists - Professional Association

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):311S-37S.

GUIDELINE AVAILABILITY

Electronic copies: Available to subscribers of the Chest - The Cardiopulmonary and Critical Care Journal.

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

Executive Summary:

- Antithrombotic and thrombolytic therapy executive summary. Chest 2008 Jun; 133:71S-109S.

Background Articles:

- Antithrombotic and thrombolytic therapy. Chest 2008 Jun; 133:110S-112S.

- Methodology for antithrombotic and thrombolytic therapy guideline development. Chest 2008 Jun; 133:113S-122S.
- Grades of recommendation for antithrombotic agents. Chest 2008 Jun; 133:123S-131S.
- Strategies for incorporating resource allocation and economic considerations. Chest 2008 Jun; 133:132S-140S.

Electronic copies: Available to subscribers of the Chest - The Cardiopulmonary and Critical Care Journal.

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on November 19, 2004. The information was verified by the guideline developer on January 12, 2005. This summary was updated by ECRI on March 6, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin sodium). This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on September 7, 2007 following the revised U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin). This summary was updated by ECRI Institute on March 14, 2008 following the updated FDA advisory on heparin sodium injection. This NGC summary was updated by ECRI Institute on November 24, 2008. The updated information was verified by the guideline developer on January 7, 2009.

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